the risk assessment of pesticides, which rely on toxicokinetic data, and on validation of currently used exposure assessment models. Further limitations currently impacting on the use of HBM in this field are a lack of large prospective cohort studies to assess long term exposure to currently used pesticides.

The evidence identified has been used to help formulate recommendations on the implementation of HBM as part of the occupational health surveillance for pesticides in Europe. Some key issues were considered that would need to be overcome to enable implementation. These included the setting of priorities for the development of new specific and sensitive biomarkers, the derivation and adoption of health-based guidance values, development of QA schemes to validate inter-laboratory measurements, good practice in field work and questionnaire design, extension of the use of biobanking and the use of HBM for post-approval monitoring of pesticide safety.

Annex C — Experience of international regulatory agencies in regards to the integration of epidemiological studies for hazard identification

C.1. WHO-International Agency for Research on Cancer (IARC)

The IARC Monographs on the Evaluation of Carcinogenic Risks to Humans of the International Agency for Research on Cancer (IARC) is a programme established four decades ago to assess environmental exposures that can increase the risk of human cancer. These include individual chemicals and chemical mixtures, occupational exposures, physical agents, biological agents, and lifestyle factors.

IARC assembles international interdisciplinary Working Groups of scientists to review and assess the quality and strength of evidence from scientific publications and perform a hazard evaluation to assess the likelihood that the agents of concern pose a cancer risk to humans. In particular, the tasks of IARC Working Group Members include the evaluation of the results of epidemiological and other experimental studies on cancer, to evaluate data on the mechanisms of carcinogenesis, and to make an overall evaluation of the carcinogenicity of the exposure to humans.

The Monographs are widely used and referenced by governments, organizations, and the public around the world to set preventive and control public health measures.

The Preamble 21 to the IARC Monographs explains the scope of the programme, the scientific principles and procedures used in developing a Monograph, the types of evidence considered and the scientific criteria that guide the evaluations. The scope of the monographs broadened to include not only single chemicals but also groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. Thus, the title of the monographs reads "Evaluation of carcinogenic risks to humans"

Relevant epidemiological studies, cancer bioassays in experimental animals, mechanistic data, as well as exposure data are critically reviewed. Only reports that have been published or accepted for publication in the openly available scientific literature are included. However, the inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results. Qualitative aspects of the available studies are carefully scrutinised.

Although the Monographs have emphasized hazard identification, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A Monograph may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies.

The structure of a Monograph includes the following sections:

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

Human epidemiological data are addressed in point 2, where all pertinent epidemiological studies are assessed. Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

The IARC evaluation of epidemiological studies includes an assessment of the following criteria: types of studies considered (e.g. cohort studies, case-control studies, correlation (or ecological) studies and intervention studies, case reports), quality of the study (e.g. bias, confounding, biological variability

[21] http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf

and the influence of sample size on the precision of estimates of effect), meta analysis and pooled analyses, temporal effects (e.g. temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure), use of biomarkers in epidemiological studies (e.g. evidence of exposure, of early effects, of cellular, tissue or organism responses), and criteria for causality.

With specific reference to causality a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality. However, it is recognized that weak associations may be important when the disease or exposure is common. Associations that are replicated in several studies of different design under different exposure conditions are more likely to represent a causal relationship than isolated observations from single studies. In case of inconsistent results among different investigations, possible reasons (e.g. differences in exposure) are sought, and high quality studies are given more weight compared to less methodologically sound ones. Risk increasing with the exposure is considered to be a strong indication of causality, although the absence of a clear dose-response effect is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure also supports a causal interpretation of the findings. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall data are considered. Biomarkers information may be used in an assessment of the biological plausibility of epidemiological observations. Randomized trials showing different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When epidemiological studies show little or no indication of an association between an exposure and cancer a judgement of lack of carcinogenicity can be made. In those cases, studies are scrutinised to assess the standards of design and analysis described above, including the possibility of bias, confounding or misclassification of exposure. In addition, methodologically sound studies should be consistent with an estimate of effect of unity for any observed level of exposure, provide a pooled estimate of relative risk near to unity, and have a narrow confidence interval. Moreover, no individual study nor the pooled results of all the studies should show any increasing risk with increasing level of exposure. Evidence of lack of carcinogenicity can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years, and latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation which summarises the results of epidemiological studies, the target organs or tissues, dose–response associations, evaluations of the strength of the evidence for human and animal data, and the strength of the mechanistic evidence.

At the end of the overall evaluation the agent is assigned to one of the following groups: Group1, the agent is carcinogenic to humans; Group 2A, the agent is probably carcinogenic to humans; Group2B, the agent is possibly carcinogenic to humans; Group 3, the agent is not classifiable as to its carcinogenicity to humans; Group 4, the agent is probably not carcinogenic to humans.

The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data. These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency).

For example, Group 1: The agent is carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Although widely accepted internationally, there have been criticisms of the classification of particular agents in the past, and more recent criticisms have been directed at the general approach adopted by IARC for such evaluations possibly motivating publication of a rebuttal (Pearce et al, 2015).

C.2. The experience of US-EPA in regards to the integration of epidemiological studies in risk assessment

The US Environmental Protection Agency's Office of Pesticide Programs (OPP) is the governmental organization in the U.S. responsible for registering and regulating pesticide products[22]. As part of this activity and prior to any permitted use of a pesticide, OPP evaluates the effects of pesticides on human health and the environment. EPA receives extensive hazard and exposure information to characterize the risks of pesticide products through the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). Information on the toxic effects of pesticides is generally derived from studies with laboratory animals conducted by pesticide registrants and submitted to EPA.

In the past, information from well-designed epidemiology studies on pesticides has not been typically available to inform EPA's evaluations of potential risks that might be associated with exposure to pesticides. With an increasing number of epidemiology studies entering the literature which explore the putative associations between pesticides exposure and health outcomes, EPA is putting additional emphases on this source of information. This is especially true for the wealth of studies deriving from the Agricultural Health Study[23] (AHS), a large, well-conducted prospective cohort study following close to 90,000 individuals over more than 20 years and from the Children's Environmental Health and Disease Prevention Research Centers. [24] EPA intends to make increasing use of these epidemiology studies in its human health risk assessment with the goal of using such epidemiological information in the most scientifically robust and transparent way.

C.2.1. OPP Epidemiological Framework Document

As an early first step in this process, EPA-OPP developed a proposed epidemiological framework document released as a draft in 2010, "Framework for Incorporating Human Epidemiologic and Incident Data in Health Risk Assessment" (US EPA, 2010a). The 2010 draft framework was reviewed favourably by the FIFRA Scientific Advisory Panel (SAP) in February, 2010 (US EPA, 2010b). This document was recently updated in 2016 to the "Office of Pesticide Programs' Framework Document for Incorporating Human Epidemiology and Incident Data in Risk Assessments for Pesticides" (US EPA, 2016). The revised and updated 2016 Framework document proposes that human information like that found in epidemiology studies (in addition to human incident databases, and biomonitoring studies) along with experimental toxicological information play a significant role in this new approach by providing insight into the effects caused by actual chemical exposures. In addition, epidemiologic/molecular epidemiological data can guide additional analyses, identify potentially susceptible populations and new health effects and potentially confirming existing toxicological observations. The concepts in the 2016 Framework are based on peer-reviewed robust principles and tools and rely on many existing guidance documents and frameworks (Table 1, below) for reviewing and evaluating epidemiology data. It is also consistent with updates to the World Health Organization/International Programme on Chemical Safety mode of action/human relevance framework which highlight the importance of problem formulation and the need to integrate information at different levels of biological organization (Meek et al, 2014). Furthermore, it is consistent with recommendations by the National Academy of Sciences' National Research Council (NAS/NRC) in its 2009 report *Science and Decisions* (NRC, 2009) in that the framework describes the importance of using problem formulation at the beginning of a complex scientific analysis. The problem formulation stage is envisioned as starting with a planning dialogue with risk managers to identify goals for the analysis and possible risk management strategies. This initial dialogue provides the regulatory context for the scientific analysis and helps define the scope of such an analysis. The problem formulation stage also involves consideration of the available information regarding the pesticide use/usage, toxicological effects of concern, exposure pathways, and duration along with key gaps in data or scientific information.

[22] See https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks for general information on pesticide science and assessing pesticide risks.
[23] See https://aghealth.nih.gov/
[24] See https://www.epa.gov/research-grants/niehsepa-childrens-environmental-health-and-disease-prevention-research-centers

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Table 11: Key guidance documents and frameworks used by OPP (from US EPA, 2016)

	1983	Risk Assessment in the Federal Government. Managing the Process
NAS	1994	Science and Judgement
	2007	Toxicity testing in the 21st Century
	2009	Science and Decisions: Advancing Risk Assessment
WHO/IPCS	2001-2007	Mode of Action / Human Relevance Framework
	2005	Chemical Specific Adjustment Factors (CSAF)
	2014	New Development in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis
EPA	1991-2005	Risk Assessment Forum Guidance for Risk Assessment (e.g. guidelines for carcinogen, reproductive, developmental, neurotoxicity, ecological, and exposure assessment, guidance for benchmark dose modelling, review of reference dose and reference concentration processes) http://www.epa.gov/risk assessment/guidance.htm
	2000	Science Policy Handbook on Risk Characterisation http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=40000006.txt
	2006	Approaches for the Application of Physiologically-Based Pharmacokinetic (PBPK) Models and Supporting Data for Risk Assessment
	2014	Framework for Human Health Risk Assessment to Inform Decision-making
	2014	Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Inter-species and Intra-species Extrapolation
	2001	Aggregate Risk Assessment https://www.epa.gov/sites/production/files/2015-07/documents/aggregate.pdf
OPP	2001 and 2002	Cumulative Risk Assessment http://www.epa.gov/ncer/cra/
OECD	2013	Organization for Economic Co-operation and Development Guidance Document on Developing and Assessing Adverse Outcome Pathways

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3590 Briefly, this EPA Framework document describes the scientific considerations that the Agency will
3591 weigh in evaluating how such epidemiological studies and scientific information can be integrated
3592 into risk assessments of pesticide chemicals and also in providing the foundation for evaluating
3593 multiple lines of scientific evidence in the context of the understanding of the adverse outcome
3594 pathway (or mode of action). The framework relies on and espouses standard practices in
3595 epidemiology, toxicology, and risk assessment, but allows for the flexibility to incorporate
3596 information from new or additional sources. One of the key components of the Agency's framework
3597 is the use the mode of action framework/adverse outcome pathway concept as a tool for organizing
3598 and integrating information from different sources to inform the causal nature of links observed in
3599 both experimental and observational studies. Mode of action (Boobis et al., 2008; Simon et al, 2014;
3600 Meek et al, 2014) and adverse outcome pathway (Ankley et al., 2010) provide important concepts in
3601 the integrative analysis discussed in the Framework document. Both a mode of action (MoA) and an
3602 adverse outcome pathway are based on the premise that an adverse effect caused by exposure to a
3603 compound can be described by a series of causally linked biological key events that result in an
3604 adverse human health outcome, and have as their goal a determination of how exposure to
3605 environmental agents can perturb these pathways, thereby causing a cascade of subsequent key
3606 events leading to adverse health effects.

3607 A number of concepts in the Framework are taken from two reports from the National Academies, *Science*
3608 *and Decisions: Advancing Risk Assessment* (NAS 2009) and *Toxicity Testing on the 21st*